Aberrant alternative splicing and extracellular matrix gene expression in mouse models of myotonic dystrophy.

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Public Summary:
The common form of myotonic dystrophy (DM1) is associated with the expression of expanded CTG DNA repeats as RNA (CUG-RNA). One idea for how this disease disrupts muscles is that the CUG-RNA is toxic because it binds up and in essence occupies the muscleblind 1 (MBNL1) protein, a key alternative splicing regulator in muscles. To test this idea, we compared the skeletal muscle of two mouse models of DM1, one expressing a CuG-RNA in their muscle and another missing their (MBNL1) genes altogether. Near identity in the abnormal splicing changes suggests that binding of MBNL1 by CUG-RNA explains >80% of the splicing pathology due to CUG-RNA toxicity. In contrast, only about half of abnormal amounts of mRNA in the CUG-RNA muscle are found when MBNL1 is deleted, indicating that CUG-RNA has effects through another protein, in particular on mRNAs for the extracellular matrix proteins that are so important for muscle structure and function. We propose that CUG-RNA causes a second separate effect that disrupts extracellular matrix mRNA regulation through a related CUG-RNA binding protein MBNL2. These findings reveal unanticipated similarities between DM1 and other muscular dystrophies, and open the way for approaches to treat DM1.

Scientific Abstract:
The common form of myotonic dystrophy (DM1) is associated with the expression of expanded CTG DNA repeats as RNA (CUG(exp) RNA). To test whether CUG(exp) RNA creates a global splicing defect, we compared the skeletal muscle of two mouse models of DM1, one expressing a CTG(exp) transgene and another homozygous for a defective muscleblind 1 (Mbnl1) gene. Strong correlation in splicing changes for approximately 100 new Mbnl1-regulated exons indicates that loss of Mbnl1 explains >80% of the splicing pathology due to CUG(exp) RNA. In contrast, only about half of mRNA-level changes can be attributed to loss of Mbnl1, indicating that CUG(exp) RNA has Mbnl1-independent effects, particularly on mRNAs for extracellular matrix proteins. We propose that CUG(exp) RNA causes two separate effects: loss of Mbnl1 function (disrupting splicing) and loss of another function that disrupts extracellular matrix mRNA regulation, possibly mediated by Mbnl2. These findings reveal unanticipated similarities between DM1 and other muscular dystrophies.